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Disease-a-Month

Differential Diagnosis of Jaundice

FRANZ J. INGELFINGER

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Disease-a-Month Series

MONTHLY CLINICAL MONOGRAPHS ON CURRENT MEDICAL PROBLEMS

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FRANZ J. INGELFINGER

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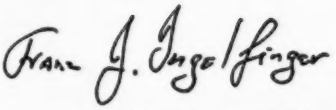

Associate Professor of Medicine, Boston University School of Medicine, was born in Germany in 1910, was brought to the United States at the age of 12, and was educated at Yale and Harvard Medical School. He learned about long intestinal tubes and subjects of allied interest in Philadelphia, where Drs. T. Grier Miller and W. Osler Abbott impressed on him that proper diagnosis and treatment of disorders of the alimentary system are impossible without knowledge as to how that system normally works. The truth of this tenet is no better exemplified than by the cogitations necessary to diagnose jaundice.

THE PHYSICIAN who would track down the cause of jaundice must, like any good sleuth, know his backgrounds and must exercise a system for apprehending the offender. Knowing his backgrounds means knowing the neighborhood of bilirubin metabolism—how it behaves normally, and when in trouble. Should trouble develop, the system gets to work. First the physician-sleuth lines up his suspects on the basis of probability and circumstantial evidence. Next comes a detailed investigation of the events leading up to the crime and meticulous inspection of the premises (i.e., the history and the physical examination). At this point, the physician may be able to identify the offender, but before making his move, he wisely checks his impressions by a series of objective tests. Often these tests not only serve as checks but are needed to help reach a diagnosis. Finally, perhaps after days of study, the doctor is ready for the arrest. Sometimes he nabs the wrong man, but more often not.

LINING UP THE SUSPECTS

Jaundice is the overt consequence of too much bile pigment in the blood and tissues. This is simple, but the disorders that

cause jaundice are intricate and many. Even the rather lengthy list in Table 1 is far from exhaustive. On the other hand, only a few conditions account for the vast majority of cases of jaundice, and, with the aid of a few definitions, a line-up of likely suspects is possible.

Let us assume that the patient is more than 5 years of age; this eliminates the somewhat different problem of jaundice in infancy. Let us also assume that the patient presents jaundice as an essential and major feature of his illness, and that jaundice is not a secondary feature of a recognized pre-existing illness. This eliminates jaundice appearing in patients with (a) obvious congestive heart failure, (b) postoperative complications, including shock and need for repeated transfusions, (c) manifest carcinomatosis and (d) overwhelming sepsis or toxemia as a result of extrahepatic and extrabiliary disease.

In the remaining cases of jaundice, the chances are over 90% that the cause will be found among the Big Five of jaundice: viral hepatitis, drug hepatitis, cirrhosis, gallstones and malignant obstruction of the common duct. If the patient is between 5 and 35 years of age, moreover, viral hepatitis by itself accounts for 90% of the cases.

TABLE 1.—DISORDERS COMMONLY RESPONSIBLE FOR JAUNDICE

I. Hemolytic Disorders*
   A. Extracorpuscular causes: infections, drugs, toxins; immune body reactions, "acquired" and "symptomatic" hemolytic anemias
   B. Intracorpuscular defects: hereditary spherocytosis, sickle cell anemia, paroxysmal nocturnal hemoglobinuria, thalassemia

II. Liver disease—predominantly hepatocellular
   A. Viral hepatitis
      1. Infectious
      2. Homologous serum
      3. Infectious mononucleosis
      4. Others (i.e., yellow fever, unknown)
   B. Bacterial hepatitis—Weil's disease
   C. Toxic hepatitis
      1. Chemical agents (carbon tetrachloride, chlorinated naphthalenes, tetrachlorethane, trinitrotoluene, chloroform, mushroom poisoning)
      2. Systemic toxemia and anoxemia (pneumonia, overwhelming infection)
   D. Hypersensitivity (drug) hepatitis (cincophen, Phenurone®,

isoniazid, Marsilid®, PAS, sulfanilamides, thiourea and derivatives)

E. Circulatory stasis and anoxia
   1. Primary (hepatic infarction, occlusion of hepatic vein)
   2. Secondary (right-sided heart failure, pulmonary infarction)

F. Unclassifiable
   1. Hepatitis of late pregnancy
   2. Dubin-Johnson syndrome
   3. Gilbert's syndrome

G. Cirrhosis
   1. Portal
   2. Postnecrotic
   3. Hemochromatosis
   4. Wilson's disease
   5. Parasitic

III. Liver disease—predominantly hepatocanalicular (intrahepatic cholestasis)
   A. Viral hepatitis (cholangiolitic hepatitis, some cases of homologous serum hepatitis)
   B. Hypersensitivity (drug) hepatitis (chlorpromazine, "Nilevar," methyl testosterone, arsenicals)
   C. Cirrhosis
      1. Primary biliary cirrhosis
      2. Secondary biliary cirrhosis

IV. Liver disease—infiltrative
   A. Carcinoma—primary
   B. Carcinoma—metastatic
   C. Lymphoma
   D. Amyloid disease
   E. Abscesses (pyogenic, parasitic)
   F. Granulomas (sarcoid, tuberculosis, brucellosis)

V. Obstruction of extrahepatic biliary system
   A. Gallstones
      1. Choledocholithiasis
      2. Choledochal obstruction related to gallstones but without stones recognized in the common duct
   B. Benign stricture (occasionally spontaneous, usually postoperative)
   C. Cancer invading ducts (primary duct cancer, cancers of pancreas or ampulla of Vater)
   D. Extrinsic compression of ducts
      1. Neoplasms of neighboring organs
      2. Enlargement of adjoining nodes
      3. Pancreatitis

*See Wintrobe, M. M.: The Anemias, *Disease-A-Month* (Chicago: The Year Book Publishers, Inc., May, 1955).

CIRCUMSTANTIAL EVIDENCE

In a case of viral hepatitis, drug hepatitis, cirrhosis or gallstones, circumstantial evidence may provide the major clue for incriminating the offender. The evidence, however, does not drop in one's lap; it has to be extracted by searching and specific questions.

Viral Hepatitis

A. *Homologous serum hepatitis* may ensue when icterogenic blood (or blood products) is transmitted from one person to another. Its incubation period is up to 6 months but usually approximates 3 months. The specific information necessary is therefore:

Has the patient within the 6 months preceding the onset of jaundice had a needle inserted into him for the purpose of

1. Injecting human serum or plasma?
2. Injecting whole human blood, or a product of human blood, excepting gamma globulin and purified albumin? Thrombin and fibrin products applied topically may also transmit virus.
3. Administering any material: analgesics, anesthetics, vitamins or even tattooing dyes? Remember to ask about anesthesia for dental work. If the patient is a narcotic addict, he may not tell you about injections.
4. Taking a blood test?

If the answer is "Yes," homologous serum hepatitis is suspect. The chances that the patient has this form of hepatitis are greatest if the purpose of using the needle was category 1 and least if category 4, with categories 2 and 3 occupying respective intermediate positions.

B. *Infectious viral hepatitis* is transmitted by fecal contamination and possibly other routes. Its incubation period averages 3 weeks but may range up to 6. Theoretically, therefore, important circumstantial evidence should be obtained by determining whether the patient was exposed, within 6 weeks preceding the onset of jaundice, to a case of jaundice, particularly to a case diagnosed as viral hepatitis. If the patient lives or works in an institution, or in a unit such as a military group, the evidence is valuable, for epidemic spread of viral hepatitis under such conditions may be striking. In the case of the average adult civilian with jaundice, however, neither a positive nor a nega-

tive history of exposure to a jaundiced person is significant. Many patients have been exposed to infectious hepatitis without knowing it because cases of nonicteric or unrecognized infectious hepatitis are prevalent, many known contacts may be jaundiced without having hepatitis, and immunity to infectious hepatitis in the adult population is high.

Drug Hepatitis

A vast number of drugs have been incriminated as inducing untoward hepatic reactions, but drug hepatitis caused by agents other than those listed in Table 1 is uncommon. For practical purposes, it is therefore important to find out if the patient in the 3 months preceding the onset of jaundice has been exposed to any of the drugs listed in Table 1 (II C and D, III B).

The most common offender is chlorpromazine, chiefly because it is such a widely used agent. If the patient has used any medication and is not sure of its nature, he should be shown the forms in which chlorpromazine is marketed. Marsilid® is rapidly attaining the position of second worst offender.

If the patient has taken any of the drugs listed, the likelihood of the drug and the jaundice being related is enhanced if the patient has taken the medication for at least 4 days, and if he was taking it at the time of onset of symptoms. On the other hand, a small total dose, or an interval of a few weeks between discontinuing the drug and the onset of jaundice does not necessarily exonerate the drug.

Exposure to certain toxins, such as carbon tetrachloride, may occur when the patient is acutely inebriated, and a history of exposure may therefore not be elicitable. If fumes of various chemicals are suspected, obviously the ventilation system under which the presumed exposure took place must be determined. Ordinary and sporadic cleaning of clothes with carbon tetrachloride-containing materials is probably a rare cause of toxic hepatitis.

Cirrhosis

A history of prolonged and heavy alcoholism is an obvious reason for suspecting cirrhosis as the cause of jaundice, but equally significant as excess consumption of alcohol is deficient and irregular intake of food. For practical purposes, "heavy alcoholism" sufficient to produce cirrhosis is that which makes

the patient skip meals, to subsist chiefly on starches or to have a low total caloric intake per day. Many times the jaundice of a patient with alcoholic cirrhosis will appear without any dramatic antecedent change in the patient's habits or fortunes. Occasionally the icterus flowers after a 2- or 3-day "bender."

Nonalcoholic forms of cirrhosis, including the postnecrotic variety, presumably are the result of some insult to the liver sustained because of viruses, parasites, toxins or unknown agents. Paradoxically, a history suggesting a previous hepatic insult is usually not obtainable in patients jaundiced because of postnecrotic cirrhosis.

Gallstones

Some patients know they have gallstones because of previous radiologic investigations. A past history suggesting episodes of biliary colic also raises the possibility of gallstones, but a past history of vague epigastric distress, belching and so-called fat intolerance has little meaning in the differential diagnosis of jaundice. In an elderly person, recurrent bouts of shaking chills and fever, if otherwise unexplained, should also suggest the possibility of gallstones, even if the chills were not accompanied by bad abdominal pain.

Jaundice appearing in a patient who has had biliary tract surgery suggests one of two possibilities:

1. If gallstones were found at the time of surgery (an important point to determine), a recurrent or residual stone may be responsible for the jaundice. This possibility is moderately enhanced if choledocholithiasis was found at the time of operation, or if common duct exploration was not carried out. An interval of more than 3 years elapsing between the biliary tract surgery and the appearance of jaundice decreases the likelihood of residual or recurrent choledocholithiasis but does not exclude the possibility.

2. If biliary tract surgery was difficult, or followed by jaundice, fever or unexpected external biliary drainage, injury of the common duct with subsequent stricture formation may have taken place. If so, any resultant cholangitis and jaundice should appear within 1 year.

Comment: The diagnostic value of circumstantial evidence has its obvious limitations. A patient known to have gallstones may fall sick of infectious hepatitis, and the patient with neoplastic obstruction of the common duct may have been taking chlorpromazine. In a given case of jaundice, however, if clinical or biochemical manifestations

and circumstantial evidence are not grossly at variance, the diagnostic implications of such evidence are best heeded. Of greatest importance is history of exposure to a needle or to a suspect drug.

Chlorpromazine may be responsible for a real diagnostic puzzle. If a patient is nauseated, then given chlorpromazine, and eventually blossoms forth with jaundice, is the chlorpromazine responsible, or was the nausea an early manifestation of an illness itself leading to jaundice? This sometimes serious dilemma is more susceptible to prevention than to solution: the use of chlorpromazine had best be avoided except under the most stringently defined indications.

HISTORY

Taking a history from a jaundiced patient essentially means finding out when and how the jaundice began, with the questions so oriented as to detect, if possible, an anamnestic pattern characterizing one of the Big Five of jaundice. The first assignment is to find out when the jaundice began.

The onset of sudden and rapidly progressive jaundice is dated with ease. When icterus begins or develops more insidiously, the task is more difficult. Many patients first become aware of jaundice when someone else notices that their skin is yellow-tinged, and this observation sometimes is not made until days, or even weeks, after the jaundice actually began.

Inquiries as to changes in the color of urine and stools are essential. The onset of jaundice, excepting the hemolytic and a few other varieties, is marked by the appearance of bile pigment in the urine before the skin or sclerae are noticeably discolored. In an observant patient, consequently, particularly if a male, the beginning of jaundice may be dated as of the time the urine turned dark (some patients describe the color as brown, reddish brown, red or "bloody"). Occasionally, the first manifestation of jaundice noticed by the patient is a light-colored stool, but this happens in less than 5% of the cases. Changes in fecal color frequently are imperceptible or, if marked, escape unnoticed.

With the date of onset of jaundice as the point of reference, symptoms that preceded or accompanied this onset are analyzed for evidence suggesting viral hepatitis, drug hepatitis, cirrhosis, gallstones or malignant obstruction of the common duct.

Viral Hepatitis

Was there a grippe-like prodrome? Most patients with viral hepatitis (nearly all with the infectious variety and somewhat

over half of those with the homologous serum type) experience symptoms before the onset of jaundice. Usually this prodromal period lasts 1-5 days, but longer and sometimes intermittent symptoms may be described by those presumed to have homologous serum hepatitis. During this time, the patient feels "punk." Specifically, he has one or more of the following complaints: lassitude, malaise, anorexia, nausea with or without vomiting, distaste for smoking, feverishness and chilliness, aching bones, various upper respiratory symptoms, constipation or loose stools, abdominal discomfort, particularly in the epigastrium and right upper quadrant, arthralgia and rashes, particularly urticaria.

Comment: Colds and grippe in various forms are common, and there is always the possibility that a cold may by pure happenstance precede jaundice not caused by viral hepatitis. Patients with neoplasia, moreover, may suffer from anorexia and malaise, and patients with gallstones may be feverish and nauseated. Because of these facts, the history of a prodrome preceding the onset of jaundice is not a 100% reliable diagnostic criterion of viral hepatitis. Nevertheless, it is a diagnostic sign which is probably as accurate as most liver function tests, and it acquires enhanced accuracy if sharply demarcated, i.e., if the period of prodromal symptoms, irrespective of their nature, is sharply demarcated from the preceding period of normal health.

Skin rashes and arthralgia, although occurring in only 5% of the cases, are of the highest diagnostic significance; that these symptoms should suddenly appear by chance a few days before jaundice not caused by hepatitis is most unlikely. If the onset of jaundice is preceded by arthralgia or urticaria, consequently, and if the patient has not been taking any medications, the chances are probably 98% that he has viral hepatitis.

Distaste for smoking has been emphasized as a point of differential diagnostic importance, but it is neither invariably present before and at the onset of viral hepatitis, nor invariably absent preceding and during jaundice from other causes. It may be credited with a D.A.* of about 90.

The absence of a grippe-like prodrome argues against infectious hepatitis, but does not exclude homologous serum hepatitis. The generalization is allowable, however, that viral hepatitis is an unlikely

*D.A. = diagnostic accuracy, and the figure expresses a percentage; i.e., in this case, the symptom indicates hepatitis with 90% accuracy. This D.A. rating is adopted in an attempt to be specific, to avoid the unending procession of "usually, often, frequently, may" and that super-hedge "not infrequently" which water down so much medical writing. But the reader must beware: these figures are *not* statistically established, and the critic who demands my references will be disappointed. These percentages merely record—and very approximately at that—the value I place on any given finding in the differential diagnosis of jaundice.

cause of jaundice in a patient who has neither a prodrome nor a history of having been stuck by a needle.

Drug Hepatitis

Drug hepatitis of the hypersensitivity type usually evokes symptoms accompanying, or preceding the onset of jaundice by a few days (3). Fever, nausea and vomiting may be striking, perhaps more so than in the average case of viral hepatitis. Arthralgias and dermal phenomena are also more common than in viral hepatitis, presumably because these symptoms express the hypersensitive state.

Drug hepatitis of the toxic variety has no characteristic qualitative features. From the quantitiative viewpoint, it may be dramatically severe and prostrating.

Comment: The onset of drug hepatitis may obviously mimic the onset of viral hepatitis. The differential point is whether or not the patient has been exposed to a potentially icterogenic drug.

Cirrhosis

In a cirrhotic patient, jaundice is rarely the only manifestations engender, in addition to jaundice, are pain, fever and chills. complaints and swelling of the abdomen or legs may precede or accompany the onset of jaundice. If present before the jaundice, however, these symptoms are so chronic and vague in onset that the patient cannot definitely state how long he has had them. The rather sharply demarcated prodrome of viral hepatitis is thus lacking.

Gallstones

The major symptoms which gallstones and their complications engender, in addition to jaundice, are pain, fever and chills. From the diagnostic viewpoint, the value of pain, if properly defined, is great, that of chills less so, and that of fever negligible.

A. Although some kind of pain may attend almost any kind of jaundice, typical *biliary colic* has diagnostic significance. Typical biliary colic is a severe pain starting epigastrically or in the right upper quadrant, mounting to maximum intensity in the course of 5 to 10 minutes, persisting from 15 to 45 minutes and radiating through to the right scapula. The whole complex

produces such agony that the patient cannot rest and may have to call the physician for relief. If a painful episode of this type precedes the onset of jaundice within a period of 3-72 hours, and the patient has previously felt well, the chances are 95% that gallstones are responsible for the icterus. Pseudogallstone colic experienced by patients with cirrhosis and hepatitis does occur but is uncommon; it is particularly uncommon in the preicteric or nonicteric phase of these diseases. Cancers almost never produce typical biliary colic. Severe pain of neoplastic origin is more likely to be persistent, and exacerbations of pain produced by hemorrhage or necrosis in a tumor mass are likely to complicate advanced stages of disease. Biliary colic followed by jaundice might, however, be closely mimicked by the occasional case of pancreatitis that is unrelated to gallstones but produces jaundice by compression of the common duct.

B. *An honest-to-goodness, bed-shaking, teeth-rattling chill* (and these are the criteria by which a chill must be defined) happens once in a while in hepatitis, but most rarely. Consequently, if real shaking chills precede the onset of jaundice, the chances are that the patient has cholangitis produced, in most cases, by common duct stones (D.A. = 90). Ulcerating neoplasms causing intermittent obstruction of the common duct—cancers of the ampulla of Vater—may cause similar cholangitis, chills and jaundice. In patients previously exposed to biliary tract surgery, stricture of the common duct must be considered.

Absence of biliary colic, chills or both does not exclude gallstones as a cause of jaundice. In some 10% of patients jaundiced because of choledochal obstruction, particularly those in older age groups, the jaundice may be "silent" or accompanied by ill-defined distress. Complete absence of pain both preceding and during the onset of jaundice is distinctly unusual in a person under 60 with a gallstone blocking the common duct.

C. Unless cholangitis is present as a complication, choledocholithiasis with jaundice does not cause *fever*. Jaundice produced by neoplastic obstruction of the common duct and by cirrhosis is often afebrile, as are certain cases of hepatitis, particularly those produced by the virus of homologous serum hepatitis. Conversely, gallstones, viral and drug hepatitis and certain cases of "active" cirrhosis with a florid inflammatory reaction may exhibit temperatures ranging between 99 and 103. It is thus apparent that neither the presence nor absence of moderate fever offers much diagnostic help in the differential

diagnosis of jaundice. High, spiking and intermittent fevers have the same significance as the shaking chills which they usually attend.

Neoplastic Obstruction of the Common Duct

Jaundice as well as other symptoms produced by neoplastic obstruction of the common duct usually begins and advances insidiously. In fact, the most positive evidence suggesting neoplastic obstruction of the common duct is the absence of historical features characterizing other types of jaundice: no history of injections, no exposure to hepatotoxic agents, no clearly demarcated prodrome, no biliary colic or chills.

The recent medical literature contains many attacks on the concept that the jaundice of neoplastic choledochal obstruction is "painless," and it is indeed true that patients so afflicted may have varying types and degrees of upper abdominal or back pain. On the other hand, to ascribe real biliary colic to neoplastic obstruction of the common duct is to stick out one's diagnostic neck. In addition, jaundice appearing gradually, painlessly and without any other clear-cut symptom in an elderly patient who has not been exposed to needles or drugs is, until proved otherwise, jaundice produced by a neoplasm invading or compressing the common duct.

Itching. Itching is believed to result from the accumulation of bile salts in the blood and tissues of a jaundiced patient. In cases of extrahepatic obstruction, hepatic parenchyma retains its ability to manufacture these salts which back up into the blood. In jaundiced patients with parenchymal damage, as in hepatitis or cirrhosis, for example, bile salt production is correspondingly impaired, and the plasma level of these salts does not become excessive even if jaundice is severe. Ideally, itching should thus characterize obstructions of the common duct but not liver disease. Some 25% of patients with choledochal obstruction, however, do not itch, and some 10% of those with liver disease do. Patients with intrahepatic cholestasis (see Abnormal Mechanisms of Bilirubin Metabolism, p. 22) due to drug sensitivity are understandably prone to pruritus. If drug ingestion can be excluded, severe unremitting itching with nasty excoriations in a jaundiced patient suggests obstruction of the hepatic or common duct (D.A. = 90). If the itching antedated the recognition of jaundice, its diagnostic value is enhanced.

PHYSICAL EXAMINATION

JAUNDICE

A. *Finding it.* That jaundice may be missed unless purposefully looked for in skin and sclerae under daylight is a hackneyed but undeniable truism. Looking at the sublingual mucous membrane has never revealed otherwise undetectable jaundice to me. In case of doubt, the suspicious observer turns to tests of bile pigment in serum and urine. A deep orange jaundice is sometimes found in severe hepatitis, particularly in certain forms of hepatic necrosis (acute yellow atrophy). In long-standing obstruction of the biliary tract, a greenish hue may develop. These shades of jaundice are interesting but only moderately significant from the diagnostic viewpoint.

B. *The severity of jaundice* at the time the patient is first seen provides little diagnostic information. Certainly the idea sometimes expressed that severe jaundice with bilirubinemia exceeding 30 mg.% is rarely caused by liver disease is fallacious. If jaundice over a period of weeks remains mild—i.e., with bilirubin levels under 10 mg.%—the diagnosis of malignant occlusion of the common duct becomes increasingly unlikely with the passage of time; the bilirubinemia produced by such occlusion usually achieves levels between 15 and 40 mg.%.

C. *The course.* Patients are always saying that their jaundice is getting worse or getting better, but beware of accepting these interpretations at face value. Sometimes the skin may really appear lighter or darker but in many cases the patient's emotional longing to get well (or depressed pessimism that he won't improve) strongly affects his impression of the intensity of his jaundice. Unless very clear-cut, consequently, changes in the degree of icterus based on the patient's or even the physician's impressions are suspect. They should be documented with laboratory tests.

The jaundice of viral hepatitis, drug hepatitis and cirrhosis rises moderately steeply, achieves a plateau of variable duration, and then drops off gradually. Should a relapse occur, however, the phase of declining bilirubinemia may be reversed abruptly. The jaundice produced by choledocholithiasis is usually transient or grossly fluctuating, but in some 10-15% of cases, the obstruction is sufficiently complete to cause a relatively steady plateau of icterus. In patients with neoplastic obstruction of the common duct, the situation is more or less the

reverse: a steady plateau of jaundice is found in some 90% of the cases, but 10% may exhibit considerable variations in the intensity of icterus. In the case of ulcerating tumors, such as those at the ampulla of Vater, fluctuations like these are usually explained by assuming that the tumor has become eroded and has established a fistulous communication between biliary tract and the gut; but in some cases of neoplastic choledochal obstruction the anatomic evidence does not account for changes in the degree of jaundice, and the pathogenesis of such changes remains mysterious.

Signs of Liver Disease

A. *The right upper abdominal quadrant.* In an average case of hepatitis, the liver edge is some 2–5 cm. below the costal margin, smooth, normally firm and tender when flipped. The cirrhotic liver is typically somewhat larger, irregular of edge, rubbery firm and relatively nontender. In many cases of hepatitis and cirrhosis, however, livers are remarkably nonconformist: they may be tiny or huge, painless or exquisitely tender. If to this intrinsic variability are added the errors introduced by the physician's not always accurate palpation, it is apparent why physical findings in the right upper abdomen of a patient with liver disease are of limited diagnostic significance. More important is what he finds elsewhere.

B. *Extrahepatic evidences indicative of liver disease* in a jaundiced patient are:

1. A disproportion between the patient's exhausted and prostrated appearance on one hand, and the lack, on the other, of fever, tachycardia, pinpoint tenderness or other clear-cut localized abnormalities.

2. Spider angiomata. These dusky red spots with their net of radiating vessels are characteristically found on the head, neck and shoulders, but don't forget to look at the arms and the hands, particularly between the fingers. Finding one or two spider angiomata is not very significant because some people have a few of these lesions even during good health. Numerous spiders, particularly if observed to appear during jaundice, indicate liver disease (D.A. = 97). Since pregnancy is another cause of spider angiomata, a pregnant woman with jaundice caused by choledocholithiasis might present a diagnostic pitfall, but recognition of the pregnancy puts the physician on guard.

3. Ascites. The finding of ascites in a jaundiced patient means liver disease except: (a) when the patient has a history and findings suggesting right-sided heart failure. In such a patient, cardiac abnormalities will exist, peripheral edema will at least accompany the ascites, and evidence of increased venous pressure will be detectable by appropriate tests. Pulmonary findings are of limited value in the differential diagnosis, since basal rales or signs of pleural fluid frequently accompany ascites of hepatogenous origin; (b) when the patient suffers cancer causing both obstruction of the common duct and peritoneal fluid. For practical purposes, this is cancer of the pancreas with peritoneal seeding; occasionally, other digestive tract neoplasms are responsible. Ovarian carcinoma, a major cause of ascites, practically never causes jaundice; (c) when the patient has liver disease complicated by a primary liver cancer.

4. Peripheral edema, with or without ascites, suggests liver disease as opposed to neoplasm or gallstones, provided a jaundiced patient does not have cardiac decompensation and has not been ill sufficiently long to permit the edema of malnutrition. Unilateral edema raises the possibility of venous or lymphatic block, perhaps complicating intra-abdominal neoplasm, particularly pancreatic.

5. The signs of hepatic coma (lethargy, drowsiness, confusion, "liver flap," frank coma and fetor hepaticus) suggest severe primary liver disease in patients with jaundice for 1 month or less. Liver damage sufficient to induce liver coma may also take place following prolonged obstruction of the common duct by stone or neoplasm, or when hepatoma complicates chronic cirrhosis. Under these circumstances, however, a history of jaundice lasting for less than 4 weeks is unlikely.

The hepatic coma that sometimes is part of an acute hepatorenal syndrome may cause confusion, for this syndrome with rapidly developing jaundice and signs of coma may attend not only Weil's disease or hepatic intoxications (i.e., carbon tetrachloride), but also essentially extrahepatic problems such as calculous obstruction of the common duct or biliary tract surgery. The hepatorenal syndrome, however, should be recognized by the impaired urinary output and the rapidly rising concentration of nonprotein nitrogen in the blood.

6. Liver palms. If the phenomenon is striking, with an intense mottled blush surrounding a pallid yellow center, and if the patient is not a victim of chronic malnutrition, this finding indicates primary liver disease with a D.A. of about 85%.

Borderline changes suggesting liver palms are best ignored.

7. Bleeding manifestations. Purpura of the skin or gross bleeding from various orifices of the body of a jaundiced patient indicates primary liver disease in a patient ill for less than 2 weeks. In jaundice of longer duration, the finding has limited significance since it may represent malabsorption of vitamin K rather than hepatic impairment.

8. Splenomegaly. An enlarged spleen in a jaundiced patient indicates liver disease as opposed to obstruction of the common duct with a D.A. of 90%. Hemolytic disorders must also be considered. Rarely, a cancer of the pancreas obstructs not only the common duct but also the splenic vein to produce congestive splenomegaly; and just as rarely a lymphoma not only enlarges the spleen but also obstructs the common duct by virtue of massive infiltration of periductal lymph nodes. With these unusual exceptions, however, splenomegaly in a jaundiced patient suggests cirrhosis, hepatitis, a hemolytic disorder or diseases such as lymphoma, tuberculosis, amyloidosis or sarcoid involving both liver and spleen diffusely.

Comment: The extrahepatic manifestations of liver disease are by and large characteristic of severe hepatitis or cirrhosis and rarely attend other major causes of jaundice unless the process is advanced. Extrahepatic signs of liver damage when seen in a patient jaundiced for 3 weeks or less thus are vitally important diagnostic guides. Absence of these signs, on the other hand, does not exclude liver disease, since liver damage in many patients with hepatitis and cirrhosis is not sufficiently severe to cause the extrahepatic physical phenomena.

Signs of Gallstones and Their Complications

A. *Tenderness, muscular spasm* or a *mass* is often discovered in the right upper abdomen of a patient jaundiced because of the complications of biliary tract calculi, i.e., cholecystitis or choledocholithiasis. Moderate tenderness is not helpful diagnostically, but exquisite tenderness, muscular spasm or both suggest that gallstones are responsible (D.A. = 75). Similar findings, however, may accompany an occasional hepatic cancer, primary or secondary, or acute vascular congestion of the liver. The absence of any tenderness and muscular guarding in the right upper abdomen argues against the complications of biliary calculi, but some 10% of cases of choledocholithiasis are remarkably free of local discomfort.

The significance of feeling a mass in the right upper abdomen depends on how well you can feel the mass. If, despite tenderness and muscular guarding, the vague outlines of an inflamed gallbladder and adherent omentum can be identified in a jaundiced patient with reasonable accuracy, cholecystitis is highly suspect.

The liver is usually not enlarged in patients jaundiced because of acute cholecystitis or choledocholithiasis. If choledochal obstruction persists for weeks, and particularly if it becomes complicated by smoldering cholangitis, the liver assumes the massive proportions of secondary biliary cirrhosis, but it takes months to do this.

B. *Absence of signs suggesting liver disease.* Ascites, spider angiomata, splenomegaly, etc., should not be discovered. Secondary biliary cirrhosis with physical evidence of liver disease is of course possible in patients with gallstones neglected in the common duct for years, but this is rare nowadays. Most patients with choledocholithiasis are subjected to operation long before biliary cirrhosis eventuates. Indeed, such biliary cirrhosis as is seen usually is the result of cutting rather than of failure to cut, the cause of the cirrhosis being maladroit surgery with stricture, cholangitis and progressive biliary cirrhosis. The proposition may thus be restated: the signs of liver disease are not likely to be found in a patient jaundiced because of gallstones or their complications except in a patient whose common duct has been exposed to surgical trauma. Another possible exception is the patient who has both portal cirrhosis and gallstones. Jaundice in this case is, however, more likely to be caused by the hepatic process than by the calculi in the gallbladder.

Signs of Neoplastic Choledochal Obstruction

A. The characteristic findings in the right upper abdomen are an *enlarged gallbladder* and a *not-so-large liver*. According to Courvoisier's law, an enlarged, nontender gallbladder palpable in the right upper quadrant of a jaundiced patient indicates neoplastic obstruction of the common duct. Provided that the examiner is reasonably sure of identifying such an enlarged gallbladder and can distinguish it from an enlarged liver or other masses, Courvoisier's law is remarkably reliable (D.A. = 98). Sometimes the globular mass of the enlarged gallbladder

can be seen more readily than it can be felt. To accomplish this, the examiner stands at the foot of the bed, oblique light is cast across the patient's abdomen, and the patient breathes deeply. The distended gallbladder may produce a bulge which clearly moves up and down in the right upper quadrant as the patient breathes.

The hepatic edge, unless involved by metastases, is smooth and relatively nontender. In the average case of neoplastic common duct obstruction, with a functioning gallbladder in place and the liver uninvolved by metastases, hepatic enlargement is not great, the liver edge rarely extending more than 1–2 fingers below the right costal margin.* If gallbladder function is excluded, however, either because of previous cholecystectomy or because the neoplasm is situated at or above the junction of cystic and hepatic ducts, massive enlargement extending more than a handbreadth below the right costal margin is to be expected.

B. The diagnostic significance of *rocky extrahepatic masses* suggesting neoplasia is obvious. Most striking in some cases are the generalized excoriations occasioned by intolerable itching.

THE LABORATORY

Each of the Big Five of jaundice presents a sufficiently typical picture that an integrated interpretation of probabilities, circumstantial evidence, history and physical examination permits reasonably accurate diagnosis in about 85% of cases of viral hepatitis, drug hepatitis, cirrhosis, gallstones and malignant obstruction of the common duct. Sometimes, however, an apparently "typical" case fools us, and in the remaining 15% of cases further evidence is needed. To check our diagnosis, or to obtain this evidence, we turn to the laboratory.

Laboratory tests, and in particular the so-called liver function tests, may, however, be more confusing than helpful unless their functional bases and limitations are appreciated. Jaundice is usually classified, as it is in the first half of this article, in terms of the responsible disease, i.e., in terms of a sick organ or a specific etiology. The results of liver function tests, on the other hand, are determined by abnormal *mechanisms,* and diseases identical as to etiology or as to organ affected are not neces-

*Schiff, on the other hand, maintains that total absence of a palpable liver also argues against obstructive jaundice due to pancreatic cancer. In 48 cases, the liver was not felt in 5, and 2 of these suffered from ascites (6).

sarily identical as to abnormal mechanisms produced. Liver function tests therefore cannot be expected to yield invariably consistent results within a given disease category.

The lack of parallelism between categories of disease and of mechanisms is no better exemplified than by the problem of differentiating "medical" and "surgical" jaundice. "Surgical" jaundice may be defined as jaundice produced by a gross lesion sufficiently accessible to be susceptible—on theoretical grounds at least—to surgical relief; in other words, growths, stones or inflammations blocking the biliary system *outside* the liver, i.e., the ampullary area, the common duct, the hepatic duct or the junctional area of right and left hepatic ducts. On the other hand, any process effectively blocking the biliary system *within* the liver, a cholangiolitis, for example, is too diffuse and microscopic to be by-passed by the surgeon's knife and needle; it is "medical" jaundice since its treatment perforce is medical.

Liver function tests, by contrast, cannot draw an imaginary line to divide obstructions of the intrahepatic biliary system* from those that are extrahepatic. If the process is purely one of obstruction of bile flow, with polygonal cells and mesenchyme unaffected, the abnormal mechanism influencing liver function tests is the same irrespective of the exact site of obstruction. Liver function tests under these circumstances yield what may be called a "cholestatic pattern" which does not distinguish between extra- and intrahepatic causes of biliary stasis.

A different pattern of liver function tests is exhibited when polygonal cells are damaged. This pattern may be called "dyscratic," for the tests are influenced by the impaired metabolism that attends polygonal cell damage. Most primary liver diseases, and in particular the various forms of hepatitis and cirrhosis, damage polygonal cells sufficiently that a dyscratic pattern emerges on performing liver function tests. In some forms of liver disease, however, such as certain cases of homologous serum or drug hepatitis, cholangiolitic hepatitis or primary biliary cirrhosis, polygonal cell damage is mild, and the abnormal mechanism of intrahepatic obstruction to bile flow predominates. In these cases, a cholestatic pattern will be revealed by liver function tests.

Liver function tests are also influenced by other mechanisms,

*The intrahepatic biliary system consists of: (1) bile capillaries (or canaliculi), which invest the polygonal cells, and which merge into (2) cholangioles (or ductules), which may be intra- or perilobular, and which converge to form (3) interlobular bile ducts. These join similar ducts to create (4) intrahepatic ducts, which in turn discharge into the right or left hepatic duct.

particularly by the mesenchymal inflammatory reaction stimulated by the disease process, and by the extent to which hepatic blood flow is altered. By and large, a mesenchymal reaction and altered hepatic blood flow attend diseases like hepatitis and cirrhosis and therefore contribute to the dyscratic pattern. An indolent cholangitis smoldering throughout the liver because of a benign obstruction of the common duct is also capable, however, of stimulating a mesenchymal response.

Hemolytic and hepatic icterogenic mechanisms provide further examples of interaction. Thus, portal cirrhosis is attended by an increased rate of red blood cell destruction; a pulmonary infarct not only embarrasses the hepatic circulation but provides an extra source of hemoglobin breakdown; and a transfusion of blood containing a high proportion of old erythrocytes may contribute to the degree of jaundice in patients with impaired hepatic function. Conversely, a primary hemolytic disorder may impose on the liver the burden of chronic anemia or may be responsible for the deposition of gallstones.

The fact that liver function tests assess mechanisms rather than diseases explains why it is senseless to use more than a certain number of well-tried and well-understood liver function tests in the differential diagnosis of jaundice. No matter how large one's battery of tests, adding more guns will merely bring down more evidence of abnormal mechanisms, and the main target of trying to differentiate between "medical" and "surgical" jaundice will not be hit.

BILIRUBIN AND UROBILINOGEN

Normal Sequence of Bile Pigment Metabolism

A. Bile pigment is produced in the reticuloendothelial (R-E) system, e.g., in liver, spleen and bone marrow, as a breakdown product of hemoglobin. Other but lesser sources, as yet unidentified, may exist as well. The pigment produced is bilirubin (free, plain and simple). Because free bilirubin is relatively water-insoluble and nonreactive (1) it is not excreted by the kidneys and (2) it gives an indirect van den Bergh reaction; i.e., it does not couple readily with the diazo reagent to yield the characteristic purple color unless the reaction is aided by the addition of methyl alcohol.

B. Free bilirubin is carried in the plasma to the liver for further processing.

C. In the liver, polygonal cells take up free bilirubi the blood and conjugate it with glucuronic acid:

$$\text{bilirubin} \xrightarrow[\text{transferase}]{\text{Uridinediphosphoglucuronic acid} +} \text{bilirubin glucuronide}$$

Bilirubin glucuronide is water soluble and chemically active.* Hence this compound, when it appears in the blood under abnormal conditions (1) can be excreted by the kidneys and (2) gives a direct van den Bergh reaction in that it couples readily and rapidly with the diazo reagent.

D. Conjugated bilirubin is excreted by the polygonal cells and thereupon passes through the branches of the intra- and extrahepatic biliary system to enter the duodenum.

E. Bilirubin glucuronide, on entering the intestine may be converted by bacterial action into relatively colorless substances conveniently grouped together under the name urobilinogen. In part, urobilinogen is absorbed into the portal blood and removed by some action of the liver. That which escapes into the systemic circulation may be excreted in urine.

Comment: In plasma, free bilirubin and conjugated bilirubin (when it accumulates in the blood of jaundiced patients) are carried loosely attached to protein, particularly albumin. This, however, is a transport phenomenon not related in any way to the intrinsic difference between free bilirubin (indirect reacting) and conjugated bilirubin (direct reacting). The idea that the two pigments differ because of a protein linkage has been abandoned.

Abnormal Mechanisms of Bilirubin Metabolism

Theoretically, jaundice might ensue from abnormal function of any or several of the processes A through D. As far as step B is concerned, however, an abnormality of bile pigment transport in the blood (i.e., an increased affinity of blood for bilirubin) is not recognized as a cause of jaundice. Essentially, then, mechanisms responsible for jaundice may be found in the R-E system,

*The end product of bilirubin conjugation is bilirubin diglucuronide since two moles of glucuronic acid conjugate with one of bilirubin. A monoglucuronide of bilirubin, or a closely related compound, has also been identified in normal blood and that of patients with liver disease and choledochal obstruction (1). Some evidence indicates that extrahepatic formation of this monoglucuronide is possible. In the van den Bergh reaction, the monoglucuronide appears to occupy a position intermediate between bilirubin and bilirubin diglucuronide, apparently contributing in part to the direct, and in part to the indirect, reacting pigment. It is also likely that bilirubin is conjugated under certain conditions with substances other than glucuronic acid.

liver (including polygonal cells and intrahepatic biliary system) and the extrahepatic bile ducts.

A. *The jaundice of hemolytic processes.* (Although jaundice produced primarily by hemolytic disorders is not here listed among the Big Five that pose major problems in the differential diagnosis of jaundice, an understanding of its mechanisms and effects in terms of bilirubin metabolism is necessary to round out the picture).

1. Mechanisms: Too much bilirubin is being delivered by the R-E system into the blood, so much, in fact, that the hepatobiliary system of bile conjugation and excretion cannot keep pace, and free bilirubin accumulates in the blood. The cause of such excess production of pigment by the R-E system is excess hemoglobin breakdown, which in turn results from excess red cell destruction. Since the chain of bilirubin metabolism is deranged before it reaches the liver, *hemolytic* jaundice is also known as *prehepatic* jaundice.

2. Results and interpretation of tests:

a. Elevated bilirubin levels in the blood, 80% or more of the pigment giving the indirect reaction. (Why not 100%, if it is all free bilirubin? Blood contains surface-active and solubilizing substances which, acting like methyl alcohol, may allow some free bilirubin to couple rapidly with the diazo reagent. For this reason, both in normal blood and in states of pure hemolytic jaundice, a small fraction of the free bilirubin present may react *as if* it were conjugated bilirubin. Bilirubin monoglucuronide may also account for some of the direct-reacting pigment.)

b. Urine is free of bile pigment.

c. Increased production in the intestine and excretion, in both stool and urine, of urobilinogen, reflecting the increased output of conjugated bilirubin into the intestines.

B. *The jaundice of liver disease.*

1. Mechanisms:

a. *Hepatocellular* or *parenchymatous jaundice* are names applied to jaundice produced chiefly by polygonal cell damage, which may derange normal bile pigment metabolism as follows:

(1) Bilirubin conjugation is impaired because of diminished transferase activity. A *pure* deficiency of this type may account for some cases of so-called Gilbert's syndrome (the purists insist it should be pronounced "gill-bears"), also known as constitutional hepatic dysfunction or familial nonhemolytic jaundice. In the more usual varieties of liver disease, impaired con-

jugation of bilirubin with glucuronic acid presumably is merely a part of more diffuse damage wreaked on all metabolic functions of the polygonal cell.

Impaired conjugation of bilirubin leads to retention of free bilirubin in the blood and, theoretically, to corresponding decreases in excretion of conjugated bilirubin, formation of urobilinogen and excretion of urobilinogen in stool and urine. These changes in urobilinogen output need further study; they may be minimal and transient.

(2) The polygonal cell may not be able to excrete conjugated bilirubin normally, and this pigment therefore regurgitates into the blood. This faulty mechanism causes conjugated bilirubin to appear in blood and urine. Decreased excretion of pigment into the intestine tends to decrease fecal and urinary urobilinogen output.

(3) The polygonal cell is not able to remove reabsorbed urobilinogen from the portal blood at normal rates. In this case, the proportion of reabsorbed urobilinogen made available for renal excretion increases, and urinary urobilinogen may be elevated in the face of decreased intestinal production and content of urobilinogen substances.

b. If the hepatic disease process affects the intrahepatic biliary system primarily, *intrahepatic cholestatic, intrahepatic obstructive* or *hepatocanalicular jaundice* is the result (5). Should this exist in completely pure form, with no influence on polygonal cell function (a theoretical possibility), only bilirubin glucuronide would accumulate in the blood, but apparently the backing up of this pigment in the polygonal cell interferes to some extent with the ability of polygonal cells to take up free bilirubin from the blood or to conjugate the free pigment. Actually, therefore, bilirubin glucuronide accumulates in the blood predominantly, but not exclusively. The urine is bile stained. If intrahepatic cholestasis is total (a real, not only theoretical possibility), no conjugated bilirubin reaches the intestine, and the concentration of fecal and urinary urobilinogen substances is nil.

c. Although pure polygonal cell deficiency may exist in the form of Gilbert's syndrome at one end of the spectrum of liver disease, and nearly pure cholestasis may be found at the other end (e.g., methyl testosterone hepatitis), the great majority of liver diseases is characterized by a variable admixture of the features of hepatocellular and hepatocanalicular jaundice.

2. Results and interpretation of tests:

a. The proportion of free to conjugated bilirubin in the blood of frankly jaundice patients with liver disease varies with the relative degrees of polygonal cell damage and intrahepatic cholestasis. Usually 30-70% of the total bilirubin is in the conjugated (direct) form. Less than 40% in the conjugated form indicates polygonal cell damage (i.e., "medical" jaundice), provided excess hemolysis is excluded. In cases of minimal icterus (1.5 mg.% bilirubinemia or less), the ratio of conjugated to total bilirubin does not have similar diagnostic implications.

b. Bile pigment is in the urine, but two exceptions are notable:

(1) Gilbert's syndrome.

(2) Mild jaundice of long duration or in a subsiding phase. In such cases, choluria may not be found even though some 25% of the blood bilirubin appears to give a direct van den Bergh reaction. Explanations are speculative: perhaps the direct reaction is an artefact reflecting a high level of solubilizing agents in the plasma; perhaps the renal threshold for conjugated bilirubin rises when jaundice persists for quite a long time.

c. The stools, depending on the degree of intrahepatic cholestasis, are normal or light in color.

d. Urinary urobilinogen output is variable since it is influenced by mechanisms that tend to alter the output in opposing directions: the degree of cholestasis, and the degree of hepatic insufficiency in removing absorbed urobilinogen from portal blood.

A strikingly high urinary urobilinogen value (over 1:100 dilution, or over 3.0 Ehrlich units [7]) is of real diagnostic value in the differential diagnosis of liver disease vs. obstructions of the common duct by stone or cancer. Patients presenting such diagnostic problems usually pass light-colored stools, indicating decreased excretion of bile into the gut with decreased urobilinogen formation and absorption into the portal blood. High urinary urobilinogen output under these circumstances suggests that the liver cells cannot handle even a small load, and such serious functional impairment is unlikely except in cases of "medical jaundice." Occasionally, acute changes in choledochal obstruction produced by a shifting gallstone or by pancreatitis may also cause massive urobilogenuria, but this is then a very transient finding.

C. *The jaundice of extrahepatic biliary tract obstruction.*

1. Mechanisms: The mechanisms are the same as those operative in conditions of intrahepatic cholestasis (see B - 1 - b).

2. Results and interpretation of tests:

a. Bilirubin levels in the blood are elevated, 50% or more of the pigment being in the form of conjugated bilirubin.

b. Bile pigment is in the urine.

c. With unremitting choledochal obstruction, stools remain light in color and urinary urobilinogen output is minimal to zero. If these findings persist for more than 3 weeks, extrahepatic biliary tract obstruction is a likely cause, such long-continued complete obstruction being attributable to liver disease in no more than 5% of cases, and the percentage is even smaller if drug hepatitis can be excluded.

Choledochal obstructions produced by gallstones or necrotic tumors of the Vaterian papilla are often intermittent or partial; variable stool color and urinary urobilinogen output is therefore to be expected. Hence, although persistently low urinary urobilinogen values argue for choledochal obstruction, a fluctuating and even a transiently high value does not exclude the diagnosis.

Comment: Since antibiotics interfere with the bacterial conversion of bilirubin glucuronide to urobilinogen, a decreased urinary urobilinogen output in a jaundiced patient receiving these agents must be evaluated accordingly.

The question is sometimes raised whether obstruction of either the right or left hepatic duct by extrinsic or intrinsic tumor causes jaundice. In some laboratory animals, ligation of ducts draining approximately half the liver does not make the animal icteric. In man, jaundice has been observed when a bile duct carcinoma blocked principally the right or left hepatic duct. Although the main channel of the other duct may have appeared patent, it is however possible that some of its tributaries may also have been obstructed.

Practical Points

A. *Tests for bile pigment in blood.* For the initial determination, and for specific purposes subsequently, the van den Bergh reaction is required to measure bilirubin concentration in the blood. On the other hand, to follow the course of a jaundiced patient, the simpler and cheaper icteric index is satisfactory provided the blood sample is not hemolyzed and the patient not carotenemic.

B. *Urine tests for bile and urobilinogen.* Crucial diagnostic information can be secured rapidly and cheaply if the physician will only carry out a few simple tests himself. In a patient seen early in his illness and not clinically icteric, for example, the presence of jaundice can be established rapidly by identifying bile pigment in his urine. The test is also useful in evaluating the patient who suffers a severe attack of pain but cannot be examined until some time later. If the patient collects all his urine during a period of 12 hours following the attack of pain, and if bile is identified in any of the collected samples, it can be accepted that the patient had transient jaundice, even if he is clinically and biochemically nonicteric 24 hours subsequently.

To test for bile in the urine, shake the sample and, under daylight type illumination, compare the color of the foam with the foam of a normal urine, covering up the liquid columns when making the comparison. If the foam is pigmented, bile may or may not be responsible. To identify bile pigments, the Harrison spot test or an Ictotest® tablet may be used.

Since the only urinary urobilinogen findings of great diagnostic significance are zero or minimal values on one hand, and extremely high values on the other, a gross test suffices in most instances. Approximately 5 ml. of a *freshly voided* urine sample are put in a test tube and 1 ml. of aldehyde reagent (2 Gm. paradimethylaminobenzaldehyde in 100 ml. of 20% HCl) added. If an intense reddish color develops (visible even in heavily bile-stained specimens) within 2 minutes, the sample has a very high urobilinogen content. If no trace of pinkish color develops, its urobilinogen concentration is negligible. The grossness of this rapid test is in part offset by the fact that the physician is examining really fresh urine; samples of urine used for routine urobilinogen determinations often sit around so long at the patient's bedside, in the utility room or in the laboratory that appreciable amounts of urobilinogen may be converted to urobilin and falsely low readings therefore obtained.

C. *Stool examination.* Direct examination of the stool for color by the physician is diagnostically more worth while than sending a sample to the laboratory, either for this purpose or to have a Schlesinger reaction performed (inspecting an aqueous fecal extract for green fluorescence after adding an alcoholic solution of zinc acetate). If the stool is not freshly passed, be sure to examine its color beneath the surface, which often darkens on exposure to light and air.

Conclusions

(Applying to the differential diagnosis of "medical" vs. "surgical" jaundice.)

A. *The ratio of "1 min. direct"* (Ducci and Watson [2] application of van den Bergh reaction) *to total plasma bilirubin suggests cholestasis from extra- or intrahepatic causes when it exceeds 80%; it suggests liver parenchymal disease when less than 40%.* In many cases of "medical" and "surgical" jaundice, unfortunately, values fall within 40-80%, a diagnostically indeterminate range. There is some evidence (1) to suggest that separation of plasma bile pigments into 3 fractions, i.e., bilirubin, bilirubin diglucuronide and what may be the monoglucuronide, may prove more informative. Before this partition becomes a clinically useful tool, however, practical analytic methods will have to be developed, and the identity of the third pigment better established.

B. *A urinary urobilinogen over 1:100 dilution or over 3.0 Ehrlich units, persisting for more than 2 days, suggests "medical" jaundice.*

C. *Acholic stools and zero (or very low) urinary urobilinogen values indicate cholestasis. If these findings persist for 3 weeks, the diagnosis of an extrahepatic obstruction or of an essentially cholestatic process within the liver is permissible.*

TEST OF HEPATIC METABOLIC AND SECRETORY FUNCTIONS

Tests Assessing Polygonal Cell Metabolic Function

A. *Mechanisms:* The polygonal cells of the liver metabolize proteins, carbohydrates and fats, and they detoxify exogenous and endogenous substances. Numerous tests, some using exogenous loads, have therefore been devised to assess the metabolic functions of hepatic parenchyma by measuring what are believed to be the products of these functions in blood and urine. The rationale of such tests in the differential diagnosis of jaundice rests on the assumptions that (1) the measured abnormality specifically reflects polygonal cell damage and (2) evidence of polygonal cell damage is specific for "medical" jaundice. Since neither of these assumptions is entirely correct, blood and urine tests of hepatic metabolism and detoxification have a corresponding inherent error.

Of procedures in this category, some that have best withstood the test of time are those related to plasma protein patterns. In general, liver disease:

1. Decreases albumin levels because the damaged polygonal cells make less of this protein.

2. Increases gamma globulin levels because of the inflammatory reaction affecting hepatic mesenchyme.

3. Variably affects other globulin moieties, for these are influenced by polygonal cell metabolism, mesenchymal reaction and the degree of cholestasis.

4. Decreases plasma levels of other proteins that are specifically synthesized by the polygonal cell, e.g., prothrombin and choline esterase.

The plasma content of choline esterase is not particularly helpful in the differential diagnosis of jaundice. It is mentioned here, however, to emphasize a difference of rationale in the measurement of different enzymes in the blood of jaundiced patients. Plasma choline esterase levels are believed to reflect *production* of this enzyme by liver cells, and the levels are decreased when these cells are sick. Other enzymes, such as transaminases are believed to *escape* from their normal intracellular habitat when liver cells are injured, with the result that plasma levels are increased.

B. *Results and interpretation of tests:*

1. Flocculation tests. Although many preparations are delicately sensitive to changes in plasma protein patterns, the *thymol turbidity* and *cephalin-cholesterol flocculation* tests are procedures that may be recommended as well tried and tested. Both these tests are significantly positive (thymol: over 6 Maclagan units; cephalin-cholesterol: 3 or 4 plus in 48 hours) in liver disease with pronounced polygonal cell damage and mesenchymal reaction. In general, the thymol tends to be positive in hepatitis, the cephalin-cholesterol test in cirrhosis. In some 40% of patients with homologous serum hepatitis, and in nearly all forms of predominantly hepatocanalicular jaundice, thymol turbidity values are normal. Conversely, a "surgical jaundice" caused, for example, by a gallstone lodged in the common duct may lead to cholangitis and sufficient mesenchymal reaction to raise plasma gamma globulins and bring about positive flocculation tests.

2. *Chemical measurement of albumin and globulin levels* with calculation of the A/G ratio theoretically parallels the re-

sults of flocculation tests, and in cirrhosis and chronic forms of hepatitis both chemical determinations and flocculation tests do point to decreased albumin and increased globulin levels in the blood. In earlier and more acute cases of hepatitis, however, flocculation tests may be grossly abnormal without chemically detectable changes in protein levels. The responsible changes in plasma protein partition are susceptible to *electrophoretic analysis,* but it is far from certain that electrophoretic technics enhance diagnostic accuracy in the differential diagnosis of jaundice. The blood of a patient with pure intrahepatic cholestasis and that of one with extrahepatic obstruction will, after all, exhibit similar plasma protein patterns, and increasing the delicacy of the analytic technic will not afford a means of differentiation.

3. In a jaundiced patient with *hypoprothrombinemia,* a parenteral vitamin K preparation (about 10 mg. of Hykinone® or Synkayvite® I.M. will do) re-establishes normal prothrombin levels if the cause of the hypoprothrombinemia is merely faulty absorption of vitamin K on the basis of deficient bile salts in the gut. Failure to get a clear-cut response to parenteral vitamin K suggests the liver cell cannot use the material and indicates "medical" jaundice (D.A. = 90). The trouble with the test is that many jaundiced patients do not have hypoprothrombinemia in the first place, since their livers are not sufficiently damaged or their enteric acholia sufficiently prolonged.

C. *Conclusions:* In the differential diagnosis of nonhemolytic jaundice:

1. A thymol turbidity test result of over 6 Maclagan units argues against extrahepatic obstruction, particularly in the absence of clinical evidence of cholangitis (i.e., chills and fever) (D.A. = 95). A result of 4 units or less argues against infectious hepatitis (D.A. = 90), but not againt homologous serum or drug hepatitis, nor against cirrhosis.

2. Cephalin flocculation tests with 3-4 plus values in 48 hours, and low albumin levels with reversed A/G ratios argue for "medical jaundice" in the absence of clinical signs of chronic inflammation, and if the illness does not exceed 3 months in length (D.A. = 90). Results of zero to 2 plus are not incompatible with a diagnosis of hepatitis; they argue moderately against cirrhosis (D.A. = 70).

Tests of Hepatic Secretion

A. *Bromsulfalein and rose bengal tests:* These dyes are excreted via the same anatomic pathways as bile pigments, namely: polygonal cells, intrahepatic bile channels and extrahepatic ducts. An abnormality of any of these pathways of bile pigment excretion will therefore also affect dye excretion, the only exception being a pure glucuronide transferase deficiency. In most cases of nonhemolytic icterus, consequently, the discovery of BSP retention provides no more information for purposes of differential diagnosis than is already furnished by the very existence of bilirubinemia. If conjugated bilirubin can't get out, BSP can't get out, and retention of the dye will not indicate whether the source of the trouble is parenchymatous, intrahepatically cholestatic or choledochally obstructive.

B. *Conclusions: The BSP and rose bengal tests are not useful in the differential diagnosis of "medical" vs. "surgical" jaundice.*

Cholesterol and Alkaline Phosphatase

Some tests reflect not only hepatic metabolic and secretory activity but possibly other mechanisms as well: perhaps, for example, the ability of surface-active agents such as bile salts to hold increased concentrations of certain substances in the blood.

A. *Cholesterol and cholesterol esters.* Normal polygonal cell activity appears necessary to maintain the normal 2:3 ratio of cholesterol esters (cholesterol plus fatty acid) to total cholesterol in the blood. Normal hepatic secretory activity prevents excessive accumulation of total cholesterol in the blood. With polygonal cell damage, the esterification mechanism is impaired, and cholesterol ester levels fall. Any concurrent impaired secretion of cholesterol is offset by impaired production, and total cholesterol levels stay normal or even fall. *In the average case of hepatitis and cirrhosis, consequently,*

Total cholesterol = 100-250 mg.%
Cholesterol esters = 33% or less of total

In cholestasis with relatively unimpaired polygonal cell function, total cholesterol rises. With respect to cholesterol esters, the normal *absolute* level is maintained, but not neces-

sarily the normal *ratio* of esterified to total cholesterol. *Thus in extrahepatic or in pure intrahepatic obstructive jaundice one may find:*

Total cholesterol = 200-700 mg.%
Cholesterol esters = 140-200 mg.%

Thus, a low ratio of esterified:total cholesterol does not exclude an essentially cholestatic process when total cholesterol is very high.

B. *Alkaline phosphatase.* The origin of the alkaline phosphatase that accumulates in the blood of some jaundiced patients has not been definitely identified. For conceptual purposes, however, the polygonal cell may be postulated as the source of the enzyme. In a patient with parenchymal damage, consequently, serum alkaline phosphatase activity does not rise appreciably, even if associated cholestasis is severe. In pure cholestasis, on the other hand, enzyme production is maintained, its secretion is prevented and serum levels of alkaline phosphatase rise.

For diagnostic purposes in nonhemolytic jaundice, alkaline phosphatase values over 10 units (Bodansky) suggest an extra- or intrahepatic cholestatic phenomenon; under 5 units, a disease of liver parenchyma (D.A. = 85). High serum alkaline phosphatase levels are also found when primary or secondary cancer involves the liver.

TESTS SUGGESTING POLYGONAL CELL INJURY

In disorders characterized by necrosis of hepatic parenchyma, the plasma content of iron, vitamin B_{12} and various enzymes increases. This fact has led to the postulate that these substances leak from injured polygonal cells into the blood and that, accordingly, the level of iron, vitamin B_{12} or certain enzymes in the blood provides an index of how many liver cells have been injured, and how severe the damage has been. The most popular procedures of this type currently in use are the *transaminase tests,* which measure the activity of enzymes concerned in the transfer of an NH_2 group from an amino acid to a keto acid, thus forming a new amino and a new keto acid. The enzyme helping to move the amino group from aspartic to ketoglutaric acid synthesizes the new amino acid, glutamic acid and the new keto acid, oxaloacetic acid. This enzyme is thus known as glutamic-oxalacetic transaminase (GOT). The en-

zyme moving amino nitrogen from alanine to ketoglutaric acid aids in the formation of glutamic acid and the keto acid, pyruvic acid. This enzyme is hence known as glutamic-pyruvic transaminase (GPT).

In liver disease, GOT and GPT tend to rise in the plasma and, in accordance with the postulated mechanism of this rise, the enzymes are elevated particularly in early and active phases of the hepatitis, when liver cell injury may be presumed to be greatest. In chronic or subsiding phases of hepatitis, or in cirrhosis, with cellular destruction presumably less, transaminase activity in the blood is increased only moderately.

GOT or GPT values above 300 units in a jaundiced patient are believed to reflect polygonal cell damage sufficiently to indicate active liver disease. Values under 300 may indicate a primarily cholestatic disorder (8). The reliability of this dividing point is, however, affected by several factors. As pointed out, a relatively low transaminase value does not exclude chronic polygonal cell damage. Furthermore, transaminases, and in particular GOT, are found not only in liver polygonal cells, and elevated values may therefore reflect injury to other tissues. Thus GOT values of up to 500 may be obtained in the plasma of patient with calculous obstruction of the common duct, especially if accompanied by cholangitis. Finally, in a purely intrahepatic cholestatic process, with little tissue reaction, transaminase levels above 200 units would not be expected.

Transaminase tests are definitely valuable in the differential diagnosis of jaundice, particularly if used in early or acute conditions. As is true of other good liver function tests, however, their results cannot be evaluated out of clinical context. They may be in error some 10-15% of the time, and they should not be expected to do the impossible.

OTHER TESTS

Hemotologic Procedures

A. *Leukocytes.* Polymorphonuclear leukopenia with a total white count under 5,000 in a jaundiced patient suggests a primary liver disease, but the D.A. is probably not above 75. Polymorphonuclear leukocytosis over 12,000 argues against the diagnosis of viral hepatitis (D.A. = 90). High white counts may be seen in drug hepatitis and in certain cases of "active," febrile portal cirrhosis. If these conditions can be ex-

cluded, a polymorphonuclear leukocytosis of over 15,000 in a jaundiced case suggests cholangitis caused either by a gallstone or a necrotic tumor at the ampulla of Vater (D.A. = 80).

A differential count is useful to detect the mononuclear predominance of viral hepatitis, the atypical mononuclear forms of infectious mononucleosis and the eosinophilia that may provide the lead to a diagnosis of drug hepatitis.

B. *Erythrocytes.* Study of erythrocytes is necessary not only to determine whether or not anemia is present but to carry out the proper hematologic procedures in case a hemolytic process is suspected.

Tests on Feces

Persistently positive tests for occult blood in the feces of a jaundiced patient suggest neoplasia, provided neither hypoprothrombinemia nor bleeding tendency from other causes is evident (D.A. = 80). Persistent slow bleeding from esophageal varices is possible but unusual.

X-rays

Roentgenologic study may proffer a number of findings well recognized as helpful in the differential diagnosis of jaundice, to wit: radiopaque gallstones; esophageal varices indicative of portal hypertension and liver disease; the pancreatic calcification of chronic pancreatitis; displacement, deformity or mucosal abnormalities of the stomach or duodenum suggesting pancreatic masses or neoplasms; and elevation or irregularities of the right diaphragm possibly reflecting intra- or perihepatic masses.

Depending on the organ in question, the apparent size of an organ as indicated by its x-ray shadow may or may not be informative. The apparent mass of the liver on a film is often grossly deceptive. On the other hand, the x-ray gives a good approximation of splenic size when the spleen is moderately enlarged, and a globular soft tissue shadow in the area of the gallbladder is consistent with either hydrops of that viscus, or, what is more likely in the presence of jaundice, represents a radiologic version of Courvoisier's law. Special films of the right upper abdomen are superior for demonstrating faint calcifications or gallbladder enlargement to so-called flat films of

the entire abdomen, and on occasion diagnostic sensitivity is enhanced by laminography.

It would be nice if the extrahepatic biliary passages could be delineated with radiopaque dye, but in most cases of jaundice, whether representing a "medical" or "surgical" cause, opacification of these passages cannot be achieved by technics current in the United States. If bilirubinemia is less than 6 mg.%, and especially if jaundice is waning, oral cholecystography or intravenous cholangiography may be tried. If the dye outlines the gallbladder or the common duct, it is unlikely that disease of these organs is responsible for the jaundice. If the dye fails to demonstrate the extrahepatic biliary tract in whole or in part, however, no diagnostic conclusions are warranted because liver disease as well as extrahepatic obstruction may account for the finding. It has been asserted that intravenous cholangiography in moderately jaundiced patients may demonstrate the extrahepatic biliary tract when oral cholecystography fails, but further experience is necessary to substantiate this belief.

SUMMARY — DIAGNOSIS IN MOST CASES

In the differential diagnosis of the Big Five of jaundice, the diagnostic accuracy rating of 85% claimed for clinical methods may be upped to 90-95% by the supportive use of laboratory procedures.

If laboratory tests are used to confirm a strong clinical impression, a few suffice: 1 minute direct and total bilirubin, bile in urine, thymol turbidity and alkaline phosphatase, for example. These tests, as well as routine blood studies, should eliminate the chance of missing an essentially hemolytic jaundice.

When the clinical indications are vague, all the tests listed in Table 2 may be performed, but if their use leaves the diagnostic skein still a snarl, additional liver function tests enjoy little hope of untangling it.

Table 3 presents major features which, *if present*, argue strongly for one diagnosis or another. If one or even two test results do not fit into an otherwise harmonious clinical and biochemical whole, forget the strays. Liver function tests measure the end result of a series of sequential or at times antagonistic functions (4), and it is unrealistic to expect of them a perfect diagnostic array. A minor clinical inconsistency may be similarly ignored. If a major clinical finding (i.e., one with a

D.A. of 90% or over) is out of line, however, diagnostic re-evaluation is in order.

The problem of "medical" jaundice presenting intrahepatic cholestasis is partly attenuated by the fact that most cases (possibly 90%) of hepatitis giving rise to a cholestatic pattern

TABLE 2.—DIAGNOSTICALLY VALUABLE RESULTS OF LIVER FUNCTION TESTS*

	DYSCRATIC PATTERN	CHOLESTATIC PATTERN
Plasma conjugated bilirubin (% of total bilirubin)	Under 40	Over 80
Stool color	Normal	Clay
Urinary urobilinogen (Dilution units)	Over 1:100	0 to 1:1
(Ehrlich units)	Over 3.0	0 to 0.3
Thymol turbidity (Maclagan units)	Over 6	Under 5
Ceph. chol. flocc. ("+" in 48 hrs.)	3-4	0-1
Alk. phosphatase (Bodansky units)	Under 7	Over 10
A/G ratio	Under 0.9	Over 1.4
Hypoprothrombinemia (If present) corrected by parenteral vit. K	No	Yes
Total plasma cholesterol (mg.%)	Under 150	Over 300
Cholesterol esters (% of total)	Under 30	
(mg.%)		Over 150
Transaminases (GOT or GPT units)	Over 400	Under 300

*When jaundice is caused by a disease essentially impairing polygonal cell function (dyscratic pattern) or impeding bile flow inside or outside the liver (cholestatic pattern). Values falling between those given in each column are "borderline" with respect to diagnostic significance.

of liver function tests are cases of drug or homologous serum hepatitis. Thus a cholestatic pattern of liver function test results in a patient exposed to neither needle nor drug is a strong argument for "surgical" jaundice.

THE TOUGH ONES

When the exploitation of clinical acumen and laboratory facilities adds up to nothing, several courses of action are pos-

TABLE 3.—Features of Major Significance in the Differential Diagnosis of Jaundice Caused by the Big Five

	Viral (Infectious or Serum) Hepatitis	Drug Hepatitis	Cirrhosis	Gallstones and Complications	Neoplastic Obstruction of Extrahepatic Biliary Tract
Circumstantial evidence	Exposure to needle puncture	Exposure to icterogenic drug	Alcoholic propensities	Previous diagnosis of gallstones	. . .
History	Well-documented prodrome	Jaundice preceded or accompanied by fever, rashes, arthralgia	. . .	Biliary colic, shaking chills	. . .
Physical examination	*Extrahepatic* signs of hepatic disease	Urticaria	*Extrahepatic* signs of hepatic disease	Exquisite RUQ tenderness, with or without vague mass	Distended, nontender gallbladder
Liver function tests	Dyscratic pattern	Dyscratic *or* cholestatic pattern	Dyscratic pattern	Cholestatic pattern	Cholestatic pattern
Other tests	Leukopenia with mononuclear predominance	Eosinophilia	Leukopenia, lymphocytosis, esophageal varices	Gallstones on x-ray, WBC over 15,000, chiefly polys	Occult blood in stools

sible: re-evaluation, utilization of such special diagnostic procedures as are available, waiting and seeing, and exploratory laparotomy.

Re-evaluation

Three explanations may account for the puzzling case of jaundice:

A. Viral hepatitis, drug hepatitis, cirrhosis, cholelithiasis or malignant choledochal obstruction *is* causing the jaundice but in such an atypical manner as to pass unrecognized.

B. The jaundice is a complication of some antecedent illness such as heart failure, metastasizing cancer, or sepsis without the antecedent cause having been detected.

C. One of the less common causes of jaundice is responsible. The methods of diagnosing jaundice caused by disorders other than the Big Five is not discussed here, but a few features that should stimulate suspicion of certain entities are listed.

1. Hemolytic disorders: Family history; past history of previous bouts of jaundice, especially if onset before age of 20; exposure to toxic agents; abdominal pain, chills and fever before or with jaundice; splenomegaly, especially if evidence of hepatobiliary disease minimal; anemia; serum bilirubin principally in free form; no bile pigment in urine.

2. Infectious mononucleosis: Patient child or young adult; prominent respiratory symptoms in prodrome; markedly injected and swollen throat with or without membrane; generalized lymphadenopathy; splenomegaly out of proportion to evidences of liver disease; abnormal mononuclear cells in blood.

3. Weil's disease: History of exposure to water possibly contaminated by rat's urine (i.e., stagnant millponds, fish or meat markets near harbor); severe prostration; myalgia; signs of renal failure associated with jaundice.

4. Hepatitis of late pregnancy: The name is self-explanatory, the outcome often fatal. Although the pathologic findings are different, the clinical manifestations are similar to those of severe viral hepatitis with marked parenchymal necrosis.

5. Dubin-Johnson syndrome: Evidences of chronic hepatitis extending over months and years but patient little incapacitated by his illness.

6. Gilbert's syndrome: Mild jaundice (chiefly free bilirubin) persisting for years without any other sign of hepatic impair-

ment by either clinical or commonly employed laboratory criteria. The main reason for recognizing this condition is to avoid labeling those who have Gilbert's syndrome with the more serious diagnosis of chronic hepatitis.

7. Hemochromatosis: Male; large liver; diabetes; pigmented skin. Jaundice usually appears only as a terminal event.

8. Wilson's disease: Family history; neurologic signs of lenticular damage; Kayser-Fleischer ring. Jaundice unusual (5% of early cases) or a late symptom.

9. Primary biliary cirrhosis: Female; cholestatic jaundice for weeks, months or years; whitish plaques of lipid deposited under eyes, on palms and fingers; nodules over knees and elbows.

10. Granulomas: History of prolonged and unexplained fever preceding jaundice; lymph nodes in neck, axilla, groin or visualized by x-ray of mediastinum; splenomegaly.

11. Tuberculosis: History of disease; x-ray evidence of active pulmonary lesion.

Special Diagnostic Procedures

With the exception of the ACTH test, special procedures require special tools and skills, but above all they require the ministrations of personnel with time to perform the tests and with the knowledge to interpret their results. Whether it is a duodenal drainage, a pancreatic function test or a liver punch biopsy, the occasional test performed sporadically by very busy and relatively inexperienced physicians, nurses or technicians is a decided flop. It had better be left undone. Even an otherwise well-trained pathologist may report misleadingly on liver punch biopsy material unless he has seen many such samples. When trained and meticulous personnel is available, however, special procedures may be used to considerable advantage in the differential diagnosis of jaundice.

A. *Duodenal drainage.*

1. Cholesterol crystals found in duodenal aspirate suggest gallstones in some 80% of jaundiced patients, and calcium bilirubinate granules half-heartedly point to the same diagnosis. Both types of sediment may form in long-standing jaundice from any cause and, conversely, neither cholesterol crystals nor bilirubinate granules are discovered in over half the cases of choledocholithiasis. For these reasons, hunting for these parti-

cles in duodenal contents has fallen into relative desuetude.

2. Finding exfoliated malignant cells has obvious diagnostic significance—if you can collect, preserve, and—above all—identify them correctly. In cases of pancreatic neoplasm, the chances of positive findings are said to be increased if the flow of pancreatic juice is stimulated by secretin.

B. *Tests of pancreatic function.* Serum pancreatic enzyme tests do not contribute much to the differential diagnosis of jaundice, although high levels of amylase or lipase suggest that a pancreatitis may be compressing the common duct, or may have developed as a complication of cholelithiasis. A qualitatively and quantitatively normal outpouring of pancreatic juice into the duodenum after secretin is given to a patient with jaundice is good evidence that the pancreas is not responsible, but abnormal results do not necessarily incriminate the pancreas.

C. *The ACTH test.* On the theory that ACTH inhibits the process of hepatitis or cirrhosis and thus reduces hyperbilirubinemia, but that the hormone does not affect the mechanism and degree of bilirubinemia when the extrahepatic biliary tract is obstructed, the response of the serum bilirubin level to ACTH administration has been proposed as a means of differentiating "medical" and "surgical" jaundice. The trouble is that the bilirubin level may fall some 10-40% when ACTH is given to a patient with pancreatic cancer, and that nothing may happen in a patient with severe hepatitis. Nevertheless, if 40 units of ACTH gel is given intramuscularly 3 times daily for 5 days, and if bilirubinemia decreases to a level less than 50% of its pre-ACTH value, a "medical" jaundice is indicated (D.A. = 90). Any other result has little diagnostic meaning.

D. *Percutaneous cholangiography.* Latin American and many European physicians use direct methods to settle the problem of demonstrating the extrahepatic biliary tract radiologically in a case of jaundice. A needle is inserted through the skin and into the gallbladder under peritoneoscopic control; radiopaque material is thereupon injected into the organ. Handsome pictures of the extrahepatic biliary system are often possible by this technic which, since it is performed under visual control, entails little risk when performed by deft hands. The same safety cannot be credited to procedures that blindly probe the liver with a transcutaneous needle in the hope of tapping a biliary radicle.

E. *Liver punch biopsy*. If the sample obtained happens to present a picture characteristic of certain infiltrative processes (e.g., neoplasm, sarcoid, tuberculosis, etc.) liver punch biopsy makes a diagnostic ten-strike. Nearly as conclusive are findings of cellular necrosis indicating severe liver damage, or the marked eosinophilic infiltration that may attend drug hepatitis. Like most other tests, however, liver punch biopsy falters when confronted with a cholestatic process of puzzling etiology; the bile stasis is evident enough but whether its cause is intra- or extrahepatic cannot be read from the histologic pattern. For this reason, I do not use punch biopsy in attempting to make a differential diagnosis in a case of marked (over 15 mg.% bilirubinemia) jaundice of the cholestatic variety. In such a case, furthermore, the usual risks of punch biopsy are slightly increased by the danger of bile leakage from the puncture site.

Waiting and Seeing

In the differential diagnosis of "medical" vs. "surgical" jaundice, waiting to see whether a diagnostic omen will appear is worth while. In particular, one looks for the signs of lessening biliary obstruction, i.e., decreased bilirubinemia, darker stools and more urinary urobilinogen. The problem is: how long can one wait? Three to 6 weeks. In the absence of fever or chills suggesting cholangitis, or of a local tender mass suggesting an active inflammatory process in the gallbladder area, no serious harm is done by waiting up to 6 weeks. Uncomplicated biliary stasis for this period does not appear to damage the liver irremediably or to such an extent that surgery becomes far more hazardous. The statistical likelihood is also very small that an interval of 6 weeks will represent the difference between neoplastic obstruction of the common duct that can be treated successfully by operation and one that cannot. To be sure, a certain risk is accepted by waiting if the patient has an extrahepatic biliary obstruction, but this risk is more than offset by the greater risk hazarded if surgical exploration is carried out in a patient with "medical" jaundice. Signs indicating that the waiting period should be shortened are fever and chills, and evidences suggesting rapidly advancing hepatic failure, such as lethargy and severe anorexia. The most important function to observe while waiting and seeing is that of the urinary tract, for renal failure may rather suddenly com-

plicate severe jaundice, particularly if an inflammatory process is part of the picture. During the waiting period, consequently, urine output and NPN or BUN should be measured repeatedly.

Exploratory Laparotomy

Exploratory laparotomy is justified when, at the end of a waiting period of 3-6 weeks, and in spite of utilizing available procedures, reasonable possibility still exists that the patient has jaundice caused by a surgically correctable lesion. The operative procedure may succeed in making a diagnosis by using routine technics of observation and probing, but in certain cases, such as tumors of the hepatic ducts within the liver, or small lesions in the ampullary area, only operative cholangiography may provide the necessary information. A liver biopsy is indicated under most circumstances, but particularly if the operative procedure fails to identify a cause for the jaundice in the extrahepatic biliary system.

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